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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,039	06/23/2005	Tetsuro Kokubo	4439-4023	8665

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,039	KOKUBO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-9 have been canceled. Claims 1 and 10 remain pending and under consideration.

The examiner for this application has changed. Please direct all future correspondences to Michael C. Wilson, Art Unit 1632.

Applicant's arguments filed 7-24-06 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Enablement

The rejection of claims 1 and 10 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of monitoring expression of a gene encoding a protein that varies a NMR signal and can be quantified by NMR, without the requirement to add an exogenous substrate, does not reasonably provide enablement for a method of monitoring expression of monitoring expression of a chosen gene, wherein the accumulation of any molecule that varies a NMR signal and can be quantified by NMR is measured has been withdrawn because the claims are limited to in vitro embodiments and because PPK expression is quantified using non-destructive NMR techniques.

In particular, claim 1 is drawn to a method of monitoring expression of any target gene by transfecting cells with a plasmid in which the PPK gene is connected inframe

and downstream of the target gene, culturing the cells, inducing PPK expression and quantifying PPK expression using non-destructive NMR without adding exogenous substrate. Claim 1 is limited to *in vitro* embodiments because the method is limited to culturing transfected cells ("culturing the transformants"). It cannot be envisioned how methods of making transgenics, i.e. *in vivo* embodiments, could be encompassed by step 3 of claim 1 as written.

Claim 10 is drawn to a method of screening a compound by transfecting cells with a plasmid in which the PPK gene is connected inframe and downstream of a target gene, culturing the cells in the presence/absence of a compound without adding exogenous substrate, inducing PPK expression, quantifying PPK expression using non-destructive NMR without adding exogenous substrate and comparing the results in the presence and absence of the compound. Claim 10 is limited to *in vitro* embodiments because the method is limited to culturing transfected cells ("culturing the transformants"). It cannot be envisioned how methods of making transgenics, i.e. *in vivo* embodiments, could be encompassed by step 3 of claim 10 as written.

It was known in the art at the time of filing that *in vivo*, non-destructive monitoring of gene expression was possible using a promoter linked to a luciferase gene (Contag, Phtochem. Photbiol., 1997, Vol. 66, pg 523-31). It was also known that numerous molecules could monitored using NMR without an exogenous substrate, such as transferrin, cytochrome-c, phosphocreatine and polyphosphate (Sharfstein, 1994, Ann NY Acad. Sci. 745:77-91, pg 80; Materials and Methods; Gropman, 2001, Curr. Neurol. Neurosci. Rep., Vol. 1:185-94, pg 189; Koretsky, 1996, Proceedings of the 4th Int. Soc.

Magnetic. Resonance Med., pg 69). However, the art teaches that it is difficult to monitor the expression of genes in tissues with high background expression. The same problems are likely to affect any chosen molecule in a method of *in vivo* monitoring.

Accordingly, the enablement rejection of claims 1 and 10 has been withdrawn in view of the amendment.

Indefiniteness

Claims 1 and 10 as amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 10 are indefinite because the phrase "quantifying the accumulation of polyphosphate having a mean value strand length equal to or less than 50 mer and produced by the transfromant after the expression has been induced" does not make sense. It appears that the phrase is intended to limit which polyphosphates are being quantified; however, the phrase does not clearly set forth the metes and bounds of the polyphosphates being quantified. It cannot be determined how to distinguish PPK made by the transformant after expression has been induced from PPK made by the transformant before expression is induced. It cannot be determined how to distinguish polyphosphates having a mean value strand length equal or less than 50 mer from those that do not.

The metes and bounds of when NMR is "non-destructive" in claims 1 and 10 are unclear.

It is unclear how "preparing a real time one-dimentional NMR profile" correlates to "quantifying the accumulation of polyphosphate" in step 4 of claims 1 and 10. It is unclear if they are separate steps or if the "preparing" further limits how the "quantifying" is performed.

The phrase "without adding an exogenous substrate" in step 4 of claims 1 and 10 is indefinite. The phrase appears to relate to how the expression of PPK is induced and not how PPK expression is quantified as claimed.

The comparison step in claim 1 (step 5) is indefinite. The comparison does not teach when a substance promotes or inhibits expression of the target gene.

New Matter

Claims 1 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "target gene" in claims 1 and 10 is new matter. Support cannot be found in the claims or specification as originally filed.

The step of "preparing a plasmid" encoding PPK "connected in frame and downstream of the target gene" is new matter. Support cannot be found in the claims or specification as originally filed.

The step of "introducing the plasmid into a host cell, a tissue or an organ, and selecting a transformant" in step 2 of claims 1 and 10 is new matter. Support cannot be found in the claims or specification as originally filed.

The step of culturing the selected transformant, and inducing expression of the PPK gene in step 3 of claims 1 and 10 is new matter. Support cannot be found in the claims or specification as originally filed.

The step of quantifying in step 4 of claims 1 and 10 is new matter. Support cannot be found in the claims or specification as originally filed.

The step of comparing in step 5 of claim 10 is new matter. Support cannot be found in the claims or specification as originally filed.

Claim Rejections - 35 USC § 102

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by {Walter (2000) PNAS 97:5151-5155} has been withdrawn. Walter quantified phosphoarginine levels in mouse skeletal muscle by non-destructive quantification of phosphate by NMR (Abstract) and taught the transformation of mouse skeletal muscle *in situ* with a recombinant adenovirus expressing phosphoarginine (Abstract; pgs. 5151-5152, Methods). Further, Walter taught that two weeks after injection of the Ad vector a unique 31P-MRS resonance was observed within injected limbs, which was not present in uninjected control limbs (Abstract; pg. 5153, Figures 2-4). Walter did not prepare a plasmid as claimed.

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by {Gropman (2001) Curr. Neurol. Neurosci. Rep. 1:185-94} has been withdrawn.

Gropman taught non-invasive screening evaluation of childhood mitochondrial diseases (pg. 189) such as Leigh Syndrome, which is caused by defective expression of cytochrome-c (pg. 187). Gropman used of NMR to analyze CSF lactate and 31P levels to diagnose a mitochondrial disorder due to defective expression of a cytochrome (pg. 190). Gropman did not quantify polyphosphate expression using NMR as claimed.

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by {Ozawa (2001) Biosci, Biotech, Biochem 65:185-189} has been withdrawn. Ozawa expressed multiheme cytochrome C and quantified expression levels using NMR (Abstract; pg. 187, Fig. 3). Ozawa did not quantify polyphosphate expression using NMR as claimed.

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Koretsky (Proceedings of the 4th Int. Soc. Magnetic. Resonance Med., 1996, pg 69) has been withdrawn. Koretsky quantified transferrin levels in mouse tumors expressing the human transferrin receptor (Introduction). Koretsky transformed mouse ear fibroblasts with a recombinant adenovirus and a DNA construct encoding human transferrin (Material and Methods). Koretsky taught mice injected with the transformed cells formed tumors that were observed in the living mice via MRI was observed within injected limbs (Material and Methods). The expression levels of the human transferring receptor were quantified in the tumor, due to transferrin's ability to bind endogenous iron, and compared to tumors in fibroblast tumors in the mice, which did not express human transferring. Koretsky did not prepare a plasmid as claimed or quantify polyphosphate expression using NMR as claimed.

Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by {Sharfstein (1994) Ann NY Acad. Sci. 745:77-91}.

Sharfstein taught transfecting cells with a plasmid encoding the polyphosphate operon, which inherently has the PPK gene connected in frame and downstream from a taret gene as claimed. The cells were selected for transformants (pg 80, Strains and plasmids; Media). PPK expression was monitored by non-destructive NMR (pg. 80; NMR spectorscopy). Sharfstein measured levels of PPX and PPK present in the E. *coli* culture conditions and the effect of PPX and PPK gene expression and/or degradation (pg. 78). Sharfstein did not use exogenous substrate to induce PPK expression.

Applicants' discussion of Sharfstein is noted but does not set forth one difference between the claims and the teachings of Sharfstein. Applicants' argue the purpose of Sharfstein was not to monitor PPK or target gene expression. Applicants' argument is moot because Sharfstein monitored PPK expression.

Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by {van Voorthuysen (2000) J. Biotech. 77:65-80}.

van Voorthuysen measured polyphosphate levels metabolism in potato plant leaves by quantification of polyphosphate via NMR (Abstract). van Voorthuysen taught transforming potato plants with a plasmid comprising a target gene operably linked in frame and down stream to a ppk gene fused to the leader sequence of a feeredoxin oxirductase gene (FNR) under the control of a leaf specific St-LS1 promoter (Abstract; pg 67, materials and methods). van Voorthuysen measured polyphosphate levels in leaf tissue from extracts made from leaf biopsies by non-destructive NMR without

adding exogenous substrate (pg 67-68, materials and methods). Without evidence to the contrary, the NMR method of van Voorthuysen is either real time, non-destructive, one-dimensional NMR or real time, non-destructive 1H-NMR as claimed.

Applicants' argue the purpose of van Voorthuysen was not to monitor gene expression. Applicants' argument is moot because van Voorthuysen monitored PPK expression. Applicants' discussion of the invention is noted but does not distinguish the claims from the teachings of van Voorthuysen.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER